FRANK J. UXA, JR.*
ROBERT D. BUYAN*
DONALD E. STOUT
KENTON R. MULLINS
LINDA ALLYSON FOX
JENNIFER K. ROSENFIELD**

OF COUNSEL:
CARLOS A. FISHER*

LAW OFFICES OF
STOUT, UXA, BUYAN & MULLINS, LLP

4 VENTURE, SUITE 300
IRVINE, CALIFORNIA 92618
(949) 450-1750
FACSIMILE: (949) 450-1764

PATENTS, TRADEMARKS, COPYRIGHTS, AND RELATED INTELLECTUAL PROPERTY MATTERS

*PROFESSIONAL CORPORATION
**ADMITTED IN MASSACHUSETTS – NOT ADMITTED IN CALIFORNIA

OUR FILE NO.

UCIVN-003C

# FACSIMILE COVER SHEET

| | |
|---|---|
| Date: | June 16, 2006 |
| To: | Examiner Carlos A. Azpuru<br>Art Unit: 1615<br>U.S. Patent and Trademark Office<br>Alexandria, VA 22313-1450 |
| Facsimile: | (571) 273-8300 |
| Re: | U.S. Patent Application No. 10/773,835<br>Filing Date: 02/05/2004<br>Inventor(s): Wong et al. |
| From: | Robert D. Buyan, Esq. |
| Total No. of Pages: | 10 (including this form). Please notify us immediately if you have not received all pages. |

---

**Attached:** Declaration pursuant to 37 C.F.R. §1.131 (3 pgs.)
Exhibit A (3 pgs.)
Exhibit B (3 pgs.)

Case No.:UCIVN-003C
Certificate of Mailing:

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of: Wong, et al. | Art Unit: 1615 |
| Serial No.: 10/733,835 | Examiner: Azpuru, Carlos A. |
| Filed: February 5, 2004`` | |
| For: Methods for Preparing and Using Implantable Substance Delivery Devices | |

**DECLARATION PURSUANT TO 37 C.F.R. § 1.131**

I, Corrinne Gail Wong, do hereby declare as follows:

1. I was previously employed by the Regents of the University of California and held an appointment as Adjunct Professor in the Department of Ophthalmology, School of Medicine, University of California Irvine (hereinafter referred to as the "University"). I have read and am familiar with the content of United States Patent Application Serial No. 10/733,835 (hereinafter referred to as the "'835 Patent Application").

2. It is my understanding that claim 35 of the '835 Patent Application reads as follows:

> 35. A method for preparing an implantable device for a sustained delivery of a substance within a body of a human or an animal subject, said method comprising the steps of:

(A) dissolving a biocompatible polymer in a suitable solvent solution to produce a polymer-solvent solution;

(B) adding said substance to said polymer-solvent solution to produce a polymer-solvent solution-substance admixture;

(C) drying said polymer-solvent solution-substance admixture to form a substantially dry mass;

(D) adding a liquid to said mass to cause said mass to soften and;

(E) manipulating said softened mass to a desired shape.

3. The method recited in claim 35 was conceived of by me and actually reduced to practice prior to June of 2000. Substance delivery implants made according to this method were subsequently used in animal studies performed at the University.

4. At least as early as 1998 I had been conducting animal studies where certain test substances were administered by intravitreal injection into the eyes of rabbits. In 1998 a decision was made to modify the study protocol to allow for intravitreal implantation of substance delivery implants containing the test substances, as well as intravitreal injection of the test substances. Also as of late 1998 or early 1999 I had begun to work on methods for preparing substance delivery implants for use in such experiments.

5. Appended hereto as Exhibit A is a true and exact copy of a protocol modification request that was prepared and signed by me in January of 1999 seeking modification of the existing study protocol to include surgical implantation of polymeric implants for sustained intravitreal delivery of growth factors VEGF and basic-FGF.

6. Appended hereto as Exhibit B is a true and exact copy of a confidential e-mail that was sent by me to other University employees on June 3, 1999 describing a method that, as of that date, had been conceived of by me and actually performed in the laboratory. This method results in preparation of implantable polymer pellets that contain growth factors VEGF and basic-FGF. Implants prepared according to this method were in fact used in subsequent animal studies conducted at the University after approval of the protocol modification requested in the document appended hereto as

Exhibit A.

I declare that all of the statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that such statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application or and patent issuing therefrom.

April 14 2006 Corinne Gail Wong
Date Corinne Gail Wong

# Exhibit "A"

ORIGINAL

**REQUEST FOR IACUC PROTOCOL MODIFICATION**
University of California, Irvine
Institutional Animal Care and Use Committee

**LR NAME:** Corinne G. Wong **PROTOCOL #** 97-1985

**PHONE NUMBER:** 824-7635 **E-MAIL ADDRESS:** cgwong@uci.edu

**MAILING ADDRESS:** Med Surge I, Room 118 **ZOT CODE:** 4375

Please check all applicable changes to be made to the approved protocol. Attach a typed narrative that describes the modification. Please refer to the modification instruction sheet for submission requirements and the details of the modification description for IACUC review. **Changes must not be implemented until IACUC approval is granted.**

Animals:
- ☐ Addition of a new species
- ☐ Addition of a new strain (including transgenics)
- ☒ Increase in the number of an already approved species (2 rabbits)
- ☐ Deletion of a species/strain from the study

Procedures:
- ☒ Addition of an invasive procedure (e.g., surgery, ICV injection)
- ☐ Addition of a non-invasive procedure (e.g., behavior test)
- ☐ Change of euthanasia methods (must be AVMA approved)
- ☐ Addition of new experimental or therapeutic agent

Personnel:
- ☐ Adding new personnel -List here:
- ☐ Deleting personnel -List here:
- ☐ Change in key personnel (e.g., Lead Researcher, surgeon, post-procedural caretaker)

Locations:
- ☐ Change of procedure/surgery rooms
- ☐ Change of housing location
- ☐ Change of mailing address, telephone, fax, email or pager numbers

Other:
- ☐ (Please describe the proposed change):

LR Signature: Corinne G. Wong Date: October 2000

Approval for inclusion of this modification into the referenced protocol has been granted by the IACUC.

Signature of IACUC Chair or designee — Date: 11/9/00

Signature ULAR Vet (Designated Review) — Date

[redacted]

**MODIFICATION OF PROTOCOL #97-1985**
CG Wong, Principal Investigator
October 2, 2000

Retinal neovascularaization (NV) is pathologic growth of new blood vessels within the retina and eventually leads to severe visual loss. Successful treatment strategies have not been developed thus far due to the lack of relevant and practical animal models. Our laboratory has developed a relevant rabbit model of retinal NV that simulates the clinical conditions of florid new blood vessel growth, hemorrhage, and subsequent retinal detachment within a practical period of time. In addition to defining the fundamental biochemical mechanisms that produce retinal NV in the relatively avascular rabbit retina, additional studies will assess classes of pharmacologic agents that may help in either preventing or slowing the rate of retinal NV.

In earlier studies that were approved under IACUC protocol #97-1985, administration of pharmacologic agents was performed by intravitreal injections of the agents dissolved in phosphate-buffered saline in a volume range between 0.025 ml (25 ul) and 0.075 ml (75 ul). Times of intravitreal needle administration either ranged at 10 to 14 days prior to surgical implantation of the sustained-release growth factors-containing pellets that induce experimental retinal NV or occurred immediately after pellet implantation through the open sclerotomy site. This sclerotomy which is approximately 1.5 mm in length then is closed with standard suturing. Generally, the concentrations of the compounds are within osmotic range that can be tolerated by the retina, which is one of the most exquisitely sensitive and metabolically active tissues in the body. "Bleaching" of the healthy reddish retina is a general non-specific indication of acute toxicity and occurs immediately if the injected agent cannot be tolerated. If bleaching is observed with any of the compounds that are introduced either with standard needle injections or diffusion from sustained-release pellets, the animal will be monitored for 15 to 30 minutes to determine if the retina is able to recover from the toxic insult. If there is no sign of recovery in this time frame, the animal will be sacrificed immediately as detailed in the original protocol.

In this new study which will require a modification of IACUC-approved protocol #97-1985, an additional step is requested where the Photogenesis surgical device will be used a second time after its first use for implantation of the sustained-release growth factor-containing pellet to induce retinal NV. This second survival surgery will be identical to the first survival surgery in all procedures so that this application is a modification of the existing project protocol rather than a new protocol submission. Moreover, this new step does not duplicate previous experiments. As with the initial procedure, this second procedure also is classified as a USDA pain category D; but no other alternatives are available as detailed in the original IACUC-approved protocol.

Specifically in the second surgical procedure, the second sustained-release pellet that will be implanted between 1 week and 6 weeks after the first implantation will contain either blanks (saline) or different classes of pharmacologic agents to combat developing retinal NV that is produced with the first pellet. In initial experiments with the Photogenesis surgical device, the rabbit eye became quiet and returned to normal within 7 days. Clinically, posterior segment surgery can be performed in time frames of 3 to 4 days with no adverse harm to the patient. Standard indirect ophthalmoscopy will be performed to monitor the eyes at 24 hrs, 48 hrs, 4, 7, 10, 14, and 21 days after surgery. Color fundus photography will document the condition of the eyes. Prophylatic treatment with vancomyin and other appropriate antiobiotics will be administered following surgery. For this new study, 2 additional rabbits are requested since in the previously approved study this same number of rabbits was sufficient to establish "proof of principle." The surgeon who will be performing these procedures is Dr. Ricardo Azevedo Ponce de Carvalho, a visiting retinal specialist from Brazil.

# Exhibit "B"

**Robert Buyan**

From: <Cgailwong@aol.com>
To: <karich@hsc.usc.edu>; <kathrynrich@yahoo.com>; <vjrajadh@uci.edu>; <rbuyan@patlawyers.com>
Cc: <Cgailwong@aol.com>
Sent: Thursday, June 03, 1999 2:56 AM
Subject: pellet supplement 2

Dear Kathy,

There seems to be a glitch. Here is another message....just in case.
Corinne

Modification of Polymeric Pellet Making Procedure to Induce Florid Retinal Neovascularization in the Rabbit
June 2, 1999
CG Wong

In order to make a polymeric pellet consisting of 8% Hydron, 40 mg of Hydron power is dissolved in 0.5 ml of 95% ethanol. All procedures are performed under sterile conditions. The Hydron powder is allowed to dissolve at room temperature with intermittent shaking before adding the slightly viscous solution directly to the growth factors VEGF and basic-FGF. Specifically, 100 ul of the 8% Hydron solution is added directly to 100 ug VEGF in a sterile vial, and the VEGF is allowed to dissolve at room temperature. Another 100 ul of the freshly made 8% Hydron solution is added to 100 ug basic-FGF in its own separate vial. The basic-FGF also is allowed to dissolve gradually at room temperature.

Then 20 ul of the dissolved VEGF in the 8% Hydron solution is aliquoted directly into a small sterile plastic beaker. The small puddle that forms at the bottom of the beaker is allowed to dry as a thin layer at room temperature in the tissue culture hood. Next, 20 ul of the dissolved b-FGF is aliquoted carefully onto the top of the dry thin layer containing the 20 ug VEGF. This solution containing 20 ug of b-FGF is allowed to dry at room temperature over the dried layer of VEGF. Between 10 and 15 ul of sterile water is aliquoted with an Eppendorf pipetteman onto the top of the dried layers containing both VEGF and b-FGF. The moistened layers are rolled gently into a small round pellet approximately 1 mm in diameter. This small pellet is rolled gently up the side of the sterile beaker so that it does not sit in the water that is left at the bottom of the plastic beaker. Then this pellet is allowed to "hang" on the side of the plastic beaker and dry ovemight at room temperature in the tissue culture hood. The pellet is used the following morning for surgical implantation over the optic disk of the rabbit.

A previous telephone conversation with Dr. Martin Friedlander at the Scripps Research Institute revolved around the possibility of combining the

growth factor VEGF with other growth factors such as b-FGF. This conversation took place sometime in January/February 1998. Dr. Friedlander stated that both he and a research fellow worked on this project for a year and "got negative results" when VEGF was combined with other growth factors and that neither of them was convinced that retinal neovascularization occurred at all. He also stated they followed the procedures that were described in the Ozaki et. al. paper. Moreover, conversations with Dr. Peter Campochiaro on this rabbit model that was developed in his laboratory indicated that he himself did not feel that this model was suitable for drug testing.. This model appeared to be reversible as described in the Ozaki et al. paper.

6/6/00

[redacted]